Dynamic Risk Stratification in Thyroid Cancer Patients:

Real Time Prognostication

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Changing Paradigms in the Management of Thyroid Cancer

“Traditional Paradigm”
One Size Fits All
Total thyroidectomy
RAI remnant ablation
All with same follow up

“Risk Adapted Paradigm”
Management recommendations based individualized risk assessment

Increased Emphasis on Assessing Risk & Predicting Outcomes
Risk Stratification

Is she a high risk or low risk patient?

- 22 year old female
- Total thyroidectomy & left MRN dissection
- 2.5 cm, multifocal, well differentiated PTC
- 20/32 lymph nodes positive
- No extrathyroidal extension
- No vascular invasion
- Post-op serum Tg 25 ng/mL (TSH 1 mIU/mL)
Potentially Important Risks

- Recurrence?
- Death from thyroid cancer?
- Complications from surgery?
- Side effects from RAI?
- Initial therapy will be ineffective?
- Distant metastases?
- Needing additional therapy?
- Disease is not RAI avid?
- Not a good Tg producer?
- FDG PET avid?
Risk Stratification in Thyroid Cancer

Static Approach

Risk of Death from Thyroid Cancer
AMES, AGES, MACIS, TNM

Diagnosis → Thyroid Surgery → RAI Ablation → Follow up
Differentiated Thyroid Cancer

Commonly Used Staging Systems
Predict risk of death, not recurrence

Mazzaferri. JCEM 2001
Risk of Persistent/Recurrent Disease

Risk Estimates Using AJCC
Total Thyroidectomy and RRA (n=588)

- AJCC I (n=281): 0% Persistent/recurrent, 1% Death
- AJCC II (n=71): 34% Persistent/recurrent, 1% Death
- AJCC III (n=89): 37% Persistent/recurrent, 1% Death
- AJCC IV (n=147): 62% Persistent/recurrent, 18% Death

Median follow up 7 yrs (1-15yrs)

Tuttle, Shaha, Thyroid 2010
Risk Stratification in Thyroid Cancer

Static Approach

Risk of Death from Thyroid Cancer
AMES, AGES, MACIS, TNM

Risk of Recurrence
ATA, LATS, ETA

Diagnosis → Thyroid Surgery → RAI Ablation → Follow up
Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

New System for Estimating Risk of Recurrence
2009 Update

**Low Risk**
- Classic PTC
- No local or distant mets
- Complete resection
- No tumor invasion
- No vascular invasion
- If given, no RAI uptake outside TB

**Intermediate Risk**
- Microscopic ETE
- Cervical LN mets
- Aggressive Histology
- Vascular invasion

**High Risk**
- Macroscopic gross ETE
- Incomplete tumor resection
- Distant Mets
- Inappropriate Tg elevation

Cooper et al, Thyroid 2009
Risk Estimates Using ATA System

Total Thyroidectomy & RRA: 1,194 patients
(Cancer centers, median follow-up 7-10 yrs)

Tuttle et al. Thyroid 2010
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

2009 ATA Risk

High Risk
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases,*

Intermediate Risk
*Aggressive histology, minor extrathyroidal extension, vascular invasion, or any involved lymph nodes*

Low Risk
*Irrathyroidal DTC*
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

2009 ATA Risk

High Risk
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases,*

Intermediate Risk
*Aggressive histology, minor extrathyroidal extension, vascular invasion, or any involved lymph nodes*

Low Risk
*Intrathyroidal DTC*
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

2009 ATA Risk

High Risk
Gross extrathyroidal extension, incomplete tumor resection, distant metastases,

Intermediate Risk
Aggressive histology, minor extrathyroidal extension, vascular invasion, or any involved lymph nodes

Low Risk
Intrathyroidal DTC

The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Randolph et al. Thyroid 2012

pN1 with extranodal extension, >3 LN involved (≈ 40%)
pN1, any LN > 3 cm (≈ 30%)

Clinical N1 (≈20%)
pN1, > 5 LN involved (≈20%)

pN1, all LN < 0.2 cm (≈5%)
pN1, ≤ 5 LN involved (≈5%)
Multifocal PMC (≈ 4-6%)

pN1 without extranodal extension, ≤ 3 LN involved (2%)
Unifocal PMC (≈ 1-2%)
The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Randolph et al. Thyroid 2012

**Modified 2009 Risks**

**High Risk**
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node > 3 cm*

**Intermediate Risk**
*Aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)*

**Low Risk**
*Intrathyroidal DTC
≤ 5 LN micrometastases (< 0.2 cm)*

**Risk of Structural Disease Recurrence**
(In patients without structurally identifiable disease after initial therapy)

- **pN1 with extranodal extension, >3 LN involved (≈ 40%)**
- **pN1, any LN > 3 cm (≈ 30%)**
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(In patients without structurally identifiable disease after initial therapy)

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High Risk
- Gross extrathyroidal extension,
- incomplete tumor resection, distant metastases,
- or lymph node >3 cm

Intermediate Risk
- Aggressive histology, minor extrathyroidal extension, vascular invasion,
- or > 5 involved lymph nodes (0.2-3 cm)

Low Risk
- Intrathyroidal DTC
- ≤ 5 LN micrometastases (< 0.2 cm)

FTC, extensive vascular invasion (≈ 30-55%)

pT3 minor ETE (≈ 3-8%)

Intrathyroidal PTC, 2-4 cm (≈ 5%)

Minimally invasive FTC (≈ 2-3%)

Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)

References in 2015 ATA Guidelines
Risk of Structural Disease Recurrence
(In patients without structurally identifiable disease after initial therapy)

**Modified 2009 Risks**

**High Risk**
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm*

**Intermediate Risk**
*Aggressive histology, minor extrathyroidal extension, vascular invasion, or > 5 involved lymph nodes (0.2-3 cm)*

**Low Risk**
*Intrathyroidal DTC, ≤ 5 LN micrometastases (< 0.2 cm)*

*While analysis of BRAF and or TERT status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available.*

PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)

PTC, extrathyroidal, BRAF mutated* (≈ 10-40%)

Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈ 10%)

Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)

Intrathyroidal unifocal PMC, BRAF mutated*, (≈ 1-2%)

References in 2015 ATA Guidelines
Risk of Structural Disease Recurrence  
(In patients without structurally identifiable disease after initial therapy)

**Modified 2009 Risks**

**High Risk**  
*Gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm*

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*Aggressive histology, minor extrathyroidal extension, vascular invasion, or >5 involved lymph nodes (0.2-3 cm)*

**Low Risk**  
*Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm)*

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**FTC, extensive vascular invasion (≈ 30-55%)**  
PT4a gross ETE (≈ 30-40%)

**pN1 with extranodal extension, >3 LN involved (≈ 40%)**

**PTC, > 1 cm, TERT mutated ± BRAF mutated* (>40%)**

**pN1, any LN > 3 cm (≈ 30%)**

**PTC, extrathyroidal, BRAF mutated* (≈ 10-40%)**

**PTC, vascular invasion (≈ 15-30%)**

**Clinical N1 (≈ 20%)**

**pN1, > 5 LN involved (≈ 20%)**

**Intrathyroidal PTC, < 4 cm, BRAF mutated* (≈ 10%)**

**pT3 minor ETE (≈ 3-8%)**

**pN1, all LN < 0.2 cm (≈ 5%)**

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**Minimally invasive FTC (≈ 2-3%)**

**Intrathyroidal, < 4 cm, BRAF wild type* (≈ 1-2%)**

**Intrathyroidal unifocal PMC, BRAF mutated*, (≈ 1-2%)**

**Intrathyroidal, encapsulated, FV-PTC (≈ 1-2%)**

**Unifocal PMC (≈ 1-2%)**

*While analysis of BRAF and or TERT status is not routinely recommended for initial risk stratification, we have included these findings to assist clinicians in proper risk stratification in cases where this information is available.*
Risk Stratification in Thyroid Cancer

Static Approach

Risk of Death from Thyroid Cancer
AMES, AGES, MACIS, TNM

Diagnosis → Thyroid Surgery → RAI Ablation → Follow up

Risk of Recurrence
ATA, LATS, ETA

Modified 2009 ATA Risk System
Risk as a Continuum
Risk Adapted Approach to Management

Real Time Prognostication

Response to Therapy Assessment

Delayed Risk Stratification

Dynamic Risk Stratification

Ongoing Risk Assessment

Tuttle, Tala, Shaha et al, Thyroid 2010

“Reconfiguring the Course”
Picture by C Emerson
Editor, Thyroid, 2010
Risk Adapted Approach to Management

Initial Static Risk Assessments
Guide initial treatment and early follow-up recommendations

Dynamic Risk Stratification
Continually modify those risk estimates as new data becomes available

Re-evaluate Management Plans
Stay the course
Testing strategy
Interventions

Momesso, Tuttle. Endo Metab Clinic NA, 2014.
Risk Adapted Approach to Management

**Initial Static Risk Assessments**
*Guide initial treatment and early follow-up recommendations*

**Dynamic Risk Stratification**
*Continually modify those risk estimates as new data becomes available*

**Important Clinical Outcomes**
- Disease specific mortality
- Recurrent/persistent disease
- Remission
- Needing additional therapy
- Distant metastases
- Non-RAI avid
- FDG avid

**Re-evaluate Management Plans**
- Stay the course
- Testing strategy
- Interventions

*Momesso, Tuttle. Endo Metab Clinic NA, 2014.*
Results That Modify Risk

Clinical utility far beyond simple disease detection

Change in serum thyroglobulin over time
Change in serum Tg antibodies over time
Results of stimulated thyroglobulin determinations
Results of follow up Neck US
Results of RAI scanning
Other cross sectional imaging
Results of FDG PET imaging
Physical examination

Tuttle. Endocrine Practice 2008.
Can any recommendations be made concerning the frequency and type of long term follow-up testing?

“Information garnered from the prior Tg response to rhTSH stimulation can form the basis of recommendations for further testing.”
R46. After the first RxWBS performed after radioiodine remnant ablation, low-risk patients with negative TSH-stimulated thyroglobulin and cervical ultrasound do not require routine DxWBS during follow-up—Recommendation A

R49. In patients with persistent disease, the serum TSH should be maintained below 0.1 mU/L indefinitely in the absence of specific contraindications—Recommendation B
**Risk Adapted Approach to Management**

**European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium**

Furio Pacini, Martin Schlumberger¹, Henning Dralle², Rossella Elisei³, Johannes W A Smit⁴, Wilmar Wiersinga⁵ and the European Thyroid Cancer Taskforce

- **Initial therapy**
  - Total thyroidectomy & RAI ablation

- **Re-evaluation**
  - 3 months and 6-12 months

- **Undetectable Tg, no other abnormalities**
  - Decrease LT4 dose
  - Yearly Tg and US

- **Detectable Tg, or other abnormalities**
  - Additional RAI
  - Surgery

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*Pacini, Eur Journal of Endocrinology, 2006*
Initial Static Risk Assessments
*Guide initial treatment and early follow-up recommendations*

Dynamic Risk Stratification
*Continually modify those risk estimates as new data becomes available*

Why is dynamic risk stratification necessary?
*Shouldn’t initial risk assessments provide all the guidance we need?*

Re-evaluate Management Plans
*Stay the course Testing strategy Interventions*

Momesso, Tuttle. *Endo Metab Clinic NA, 2014.*
Why do initial risk models predict final clinical outcomes so poorly?

Errors in Initial Risk Stratification
- Histology
- Inadequate initial staging

Biological Behavior Is Not Always Predictable
- Poorly differentiated thyroid cancers
- Follicular cancers with wide extensive vascular invasion

Impact of Therapy
- Completeness of initial surgery
- RAI avidity
- TSH responsiveness
Describing Best Response to Initial Therapy

25 yr old male
Total thyroidectomy & RAI ablation
3.5 cm tall cell variant PTC, 14/19 LN + (2.5 cm, +ENE)

<table>
<thead>
<tr>
<th></th>
<th>Excellent</th>
<th>Biochemical</th>
<th>Structural</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td>Tg &lt;0.2</td>
<td>Tg 15</td>
<td>Tg 15</td>
<td>Tg &lt;0.2</td>
</tr>
<tr>
<td></td>
<td>TgAb neg</td>
<td>TgAb neg</td>
<td>TgAb neg</td>
<td>TgAb +</td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>Tg 9</td>
<td>Tg 20</td>
<td>Tg &lt;0.2</td>
</tr>
<tr>
<td></td>
<td>Tg &lt;0.2</td>
<td>TgAb neg</td>
<td>TgAb neg</td>
<td>TgAb +</td>
</tr>
<tr>
<td></td>
<td>TgAb neg</td>
<td>US neg</td>
<td>US +</td>
<td>US +/-</td>
</tr>
<tr>
<td></td>
<td>US neg</td>
<td>Imaging neg</td>
<td>Imaging +</td>
<td>Imaging +/-</td>
</tr>
<tr>
<td></td>
<td>12 mo</td>
<td>Tg 5</td>
<td>Tg 35</td>
<td>Tg &lt;0.2</td>
</tr>
<tr>
<td></td>
<td>Tg &lt;0.2</td>
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<td>Imaging +/-</td>
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Risk Estimates Using Response to Therapy Assessment

Total Thyroidectomy and RRA (n=471, MSKCC, median F/U 7 yrs)

- **Excellent (n=159)**: 96%
- **Indeterminate (n=95)**: 87%
- **Biochemical Incomplete (n=63)**: 68%
- **Structural Incomplete (n=129)**: 37% (Persistent Biochemical), 38% (Persistent Structural), 15% (Recurrence), 0% (Death)

Bar graph showing outcomes at final follow up (%)

- **NED**: 96%
- **Persistent Biochemical**: 37%
- **Persistent Structural**: 38%
- **Recurrence**: 15%
- **Death**: 0%

*Vaisman, Shaha, Tuttle, Thyroid, 2011*

Median follow up 7 yrs
Using Response to Therapy Categories to Describe Clinical Status at Any Time Point

25 yr old male
Total thyroidectomy & RAI ablation
3.5 cm tall cell variant PTC, 14/19 LN + (2.5 cm, +ENE)

ATA 2009 Intermediate Risk Patient
AJCC Stage I

3 mo
- Tg 0.3
- TgAb +
- Indeterminate Response

6 mo
- Tg 4
- TgAb rising
- US neg
- Biochemical Incomplete Response

12 mo
- Tg 8
- TgAb rising
- Imaging +
- Structural Incomplete Response
## Using Response to Therapy to Guide Clinical Management

<table>
<thead>
<tr>
<th>Response</th>
<th>Expected Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>1-4% recurrence</td>
</tr>
<tr>
<td></td>
<td>&lt;1% death</td>
</tr>
<tr>
<td>Biochemical Incomplete</td>
<td>&gt;30% spontaneously resolve</td>
</tr>
<tr>
<td></td>
<td>20% develop structural disease</td>
</tr>
<tr>
<td></td>
<td>&lt;1% death</td>
</tr>
<tr>
<td>Structural Incomplete</td>
<td>50-85% will have persistent disease despite additional treatments</td>
</tr>
<tr>
<td></td>
<td>Nearly all deaths arise from this group</td>
</tr>
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<table>
<thead>
<tr>
<th>Response</th>
<th>Expected Outcomes</th>
<th>Clinical Implications</th>
</tr>
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<tbody>
<tr>
<td>Excellent</td>
<td>1-4% recurrence</td>
<td>Decrease intensity and frequency of follow up and degree of TSH suppression.</td>
</tr>
<tr>
<td></td>
<td>&lt;1% death</td>
<td></td>
</tr>
<tr>
<td>Biochemical</td>
<td>&gt;30% spontaneously resolve</td>
<td>Observation with stable/decreasing Tg and TgAb.</td>
</tr>
<tr>
<td>Incomplete</td>
<td>20% develop structural disease</td>
<td>Rising Tg or TgAb should prompt additional investigations.</td>
</tr>
<tr>
<td></td>
<td>&lt;1% death</td>
<td></td>
</tr>
<tr>
<td>Structural</td>
<td>50-85% will have persistent disease despite additional treatments</td>
<td>Some require additional treatments.</td>
</tr>
<tr>
<td>Incomplete</td>
<td>Nearly all deaths arise from this group</td>
<td>Some can be followed with observation depending on the specifics of the individual case.</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>20% develop structural disease</td>
<td>Continued observation with mild TSH suppression.</td>
</tr>
<tr>
<td></td>
<td>&lt;1% death</td>
<td></td>
</tr>
</tbody>
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Response To Therapy Definitions

Excellent Response
No clinical, biochemical, or structural evidence of disease

Biochemical Incomplete Response
Persistent abnormal thyroglobulin values in the absence of localizable disease

Structural Incomplete Response
Persistent or newly identified loco-regional or distant metastases

Indeterminate Response
Non-specific biochemical or structural findings which cannot be confidently classified as either benign or malignant

### Response To Therapy Definitions

*Tg cut points based on initial therapy*

<table>
<thead>
<tr>
<th></th>
<th>Total Thyroidectomy &amp; RAI ablation</th>
<th>Total Thyroidectomy</th>
<th>Lobectomy</th>
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</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>Tg &lt;0.2</td>
<td>Tg &lt;0.2</td>
<td>Tg &lt;30</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Tg 0.2-1.0</td>
<td>Tg 0.2-5.0</td>
<td>-</td>
</tr>
<tr>
<td>Biochemical Incomplete</td>
<td>Tg &gt;1.0</td>
<td>Tg &gt;5.0</td>
<td>Tg &gt;30</td>
</tr>
</tbody>
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*Momesso, Tuttle. Endo Metab Clin North American, 2014*
Risk Estimates Using Response to Therapy Assessment
Total WITHOUT RAI ablation (n=320, MSKCC and Brazil)

Median follow up 8 yrs

Momesso, Vaisman, Tuttle, in review 2016
### Risk Estimates Using Response to Therapy Assessment

**Thyroid Lobectomy (n=187, MSKCC and Brazil)**

<table>
<thead>
<tr>
<th>Outcome at final follow up (%)</th>
<th>NED</th>
<th>Recurrent/Persistent Structural Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent (n=125)</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Indeterminate (n=46)</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Biochemical Incomplete (n=12)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Structural Incomplete (n=4)</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**Median follow up 8 yrs**

*Momesso, Vaisman, Tuttle, in review 2016*
Initial Static Risk Assessments
*Guide initial treatment and early follow-up recommendations*

Dynamic Risk Stratification
*Continually modify those risk estimates as new data becomes available*

Old Concept
New Names
Validated/Operationalized
Personalized, Individualized
Thyroid Cancer Management

Re-evaluate Management Plans
Stay the course
Testing strategy
Interventions

Momesso, Tuttle. Endo Metab Clinic NA, 2014.